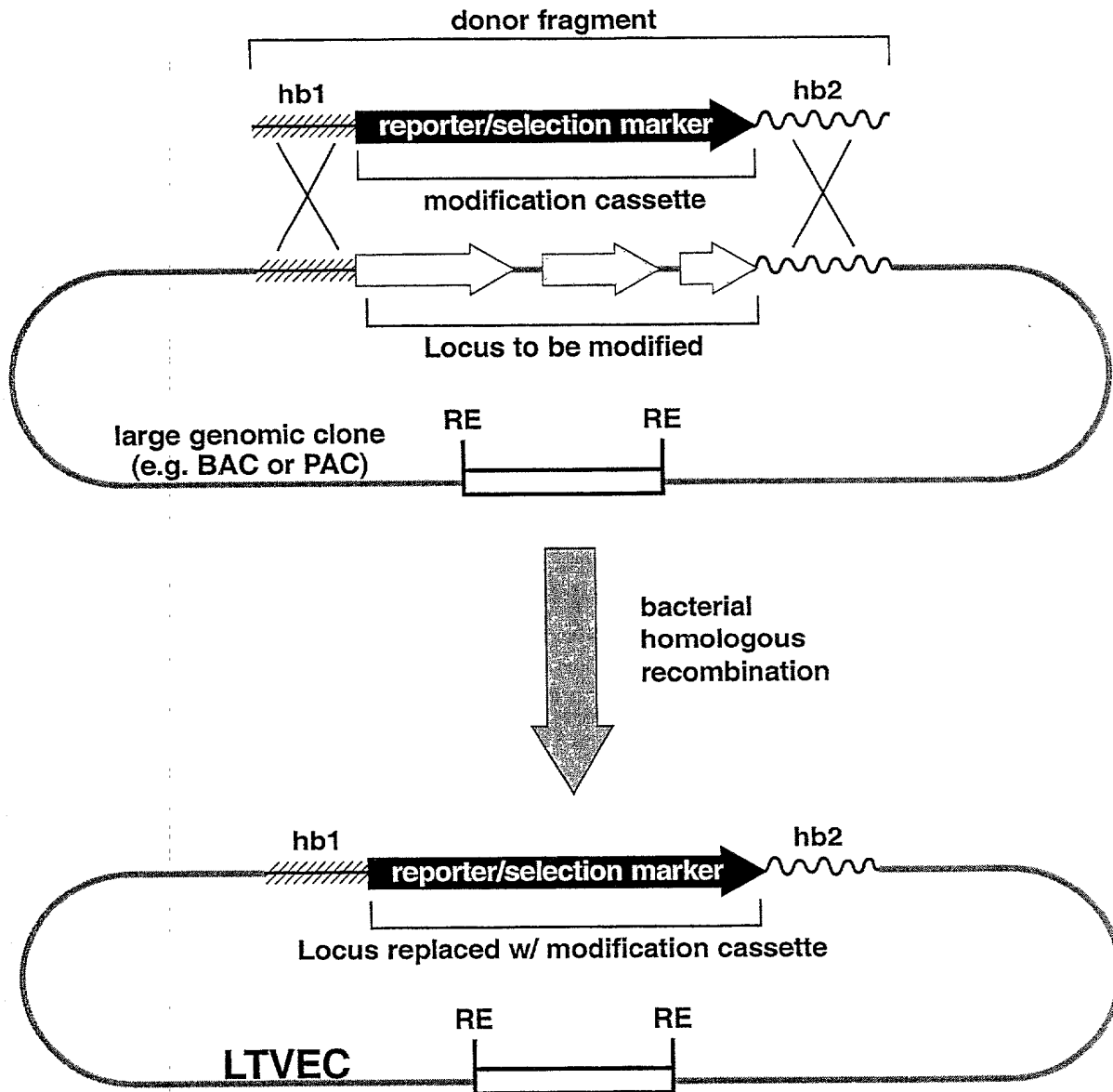
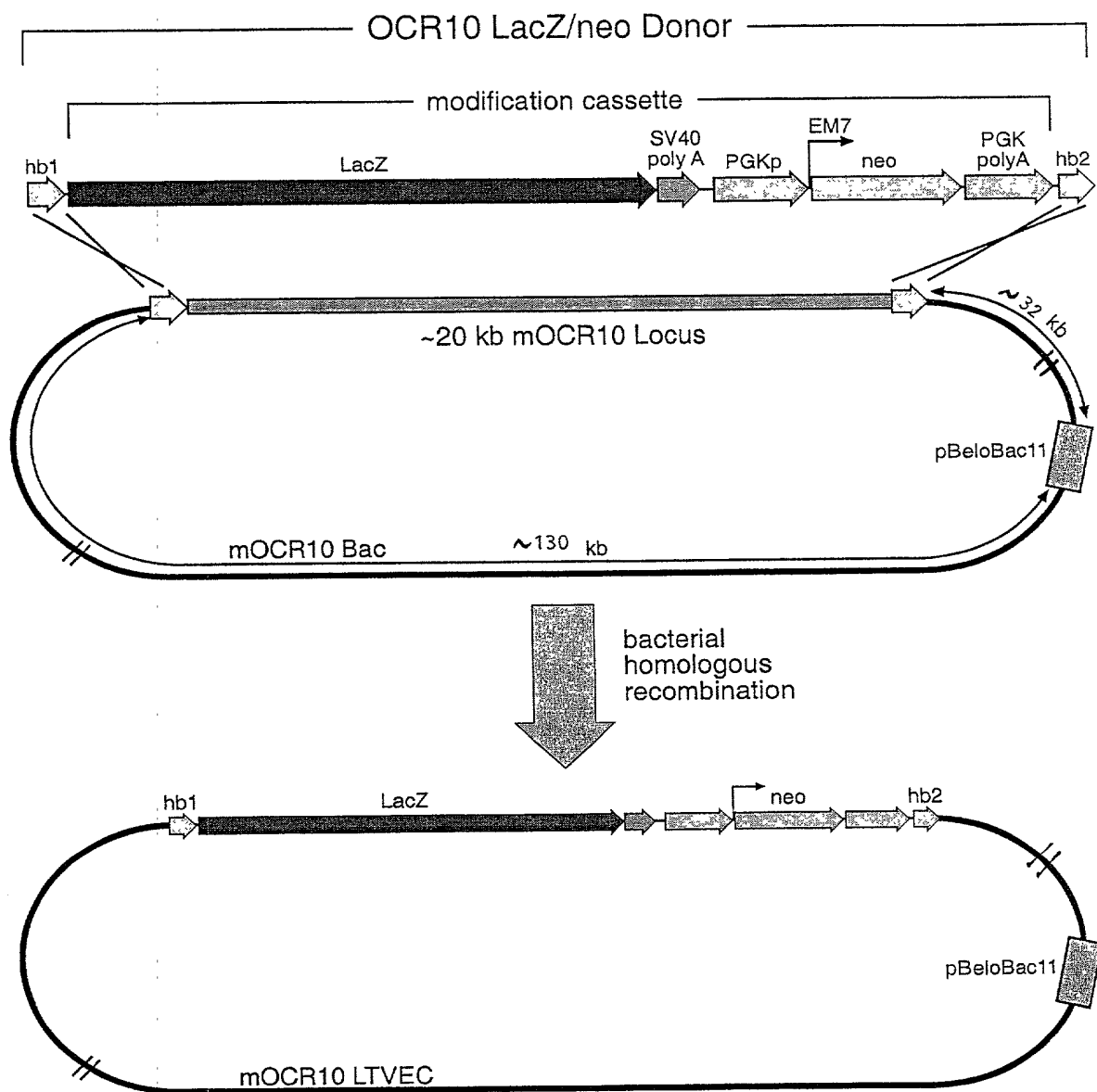


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Figure 1



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Figure 2



Att. Docket No. REG 780D
Inventors: Andrew J. Murphy, et al.
Title: METHODS OF MODIFYING
EUKARYOTIC CELLS

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FIGURE 3A

10 20 30 40 50 60
CCCCGGGCTT CCTGTTCTAA TAAGAATACC TCCTAGGTCC CCCATGGGCT AACCTCATCT
GGGGCCCCGAA GGACAAGATT ATTCTTATGG AGGATCCAGG GGGTACCCGA TTGGAGTAGA

70 80 90 100 110 120
TTGGTACTCA ACAGGGGTCT TCTTTATGAG CTTCGGACCA GCTCTTTTGA TGTGGCAGGG
AACCATGAGT TGTCCCCAGA AGAAATACTC GAAGCCTGGT CGAGAAACT ACACCGTCCC

130 140 150 160 170 180
ACTGACCCTG GGTGGGGAAG CCACTCAGTG CATGAOCCCA GCTGGTTTAC CACATATAACC
TGACTGGGAC CCACCCCTTC GGTGAGTCAC GTACTGGGGT CGACCAAGTG GTGTATATGG

190 200 210 220 230
ACATACTTTT CTTCGAGGTC TGGGACACAG C ATG CCC CGG GGC CCA GTG GCT GCC
TGTATGAAAA GAACGTCCAG ACCCTGTGTC G TAC GGG GCC CCG GGT CAC CGA CGG
Met Pro Arg Gly Pro Val Ala Ala>

240 250 260 270 280
TTA CTC CTG CTG ATT CTC CAT GGA GCT TGG AGC TGC CTG GAC CTC ACT
AAT GAG GAC GAC TAA GAG GTA CCT CGA ACC TCG ACG GAC CTG GAG TGA
Leu Leu Leu Leu Ile Leu His Gly Ala Trp Ser Cys Leu Asp Leu Thr>

290 300 310 320 330
TGC TAC ACT GAC TAC CTC TGG ACC ATC ACC TGT GTC CTG GAG ACA CGG
ACG ATG TGA CTG ATG GAG ACC TGG TAG TGG ACA CAG GAC CTC TGT GCC
Cys Tyr Thr Asp Tyr Leu Trp Thr Ile Thr Cys Val Leu Glu Thr Arg>

340 350 360 370
AGC CCC AAC CCC AGC ATA CTC AGT CTC ACC TGG CAA GAT GAA TAT GAG
TCG GGG TTG GGG TCG TAT GAG TCA GAG TGG ACC GTT CTA CTT ATA CTC
Ser Pro Asn Pro Ser Ile Leu Ser Leu Thr Trp Gln Asp Glu Tyr Glu>

380 390 400 410 420
GAA CTT CAG GAC CAA GAG ACC TTC TGC AGC CTA CAC AAG TCT GGC CAC
CTT GAA GTC CTG GTT CTC TGG AAG ACG TCG GAT GTG TTC AGA CCG GTG
Glu Leu Gln Asp Gln Glu Thr Phe Cys Ser Leu His Lys Ser Gly His>

430 440 450 460 470
AAC ACC ACA CAT ATA TGG TAC ACG TGC CAT ATG CGC TTG TCT CAA TTC
TTG TGG TGT GTA TAT ACC ATG TGC ACG GTA TAC GCG AAC AGA GTT AAG
Asn Thr Thr His Ile Trp Tyr Thr Cys His Met Arg Leu Ser Gln Phe>

480 490 500 510 520
CTG TCC GAT GAA GTT TTC ATT GTC AAC GTG ACG GAC CAG TCT GGC AAC
GAC AGG CTA CTT CAA AAG TAA CAG TTG CAC TGC CTG GTC AGA CCG TTG
Leu Ser Asp Glu Val Phe Ile Val Asn Val Thr Asp Gln Ser Gly Asn>

530 540 550 560 570
AAC TCC CAA GAG TGT GGC AGC TTT GTC CTG GCT GAG AGC ATC AAG CCA
TTG AGG GTT CTC ACA CCG TCG AAA CAG GAC CGA CTC TCG TAG TTC GGT
Asn Ser Gln Glu Cys Gly Ser Phe Val Leu Ala Glu Ser Ile Lys Pro>

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FIGURE 3B

580 590 600 610
GCT CCC CCC TTG AAC GTG ACT GTG GCC TTC TCA GGA CGC TAT GAT ATC
CGA GGG GGG AAC TTG CAC TGA CAC CGG AAG AGT CCT GCG ATA CTA TAG
Ala Pro Pro Leu Asn Val Thr Val Ala Phe Ser Gly Arg Tyr Asp Ile>

620 630 640 650 660
TCC TGG GAC TCA GCT TAT GAC GAA CCC TCC AAC TAC GTG CTG AGA GGC
AGG ACC CTG AGT CGA ATA CTG CTT GGG AGG TTG ATG CAC GAC TCT CCG
Ser Trp Asp Ser Ala Tyr Asp Glu Pro Ser Asn Tyr Val Leu Arg Gly>

670 680 690 700 710
AAG CTA CAA TAT GAG CTG CAG TAT CGG AAC CTC AGA GAC CCC TAT GCT
TTC GAT GTT ATA CTC GAC GTC ATA GCC TTG GAG TCT CTG GGG ATA CGA
Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Leu Arg Asp Pro Tyr Ala>

720 730 740 750 760
GTG AGG CCG GTG ACC AAG CTG ATC TCA GTG GAC TCA AGA AAC GTC TCT
CAC TCC GGC CAC TGG TTC GAC TAG AGT CAC CTG AGT TCT TTG CAG AGA
Val Arg Pro Val Thr Lys Leu Ile Ser Val Asp Ser Arg Asn Val Ser>

770 780 790 800 810
CTT CTC CCT GAA GAG TTC CAC AAA GAT TCT AGC TAC CAG CTG CAG ATG
GAA GAG GGA CTT CTC AAG GTG TTT CTA AGA TCG ATG GTC GAC GTC TAC
Leu Leu Pro Glu Glu Phe His Lys Asp Ser Ser Tyr Gln Leu Gln Met>

820 830 840 850
CGG GCA GCG CCT CAG CCA GGC ACT TCA TTC AGG GGG ACC TGG AGT GAG
GCC CGT CGC GGA GTC GGT CCG TGA AGT AAG TCC CCC TGG ACC TCA CTC
Arg Ala Ala Pro Gln Pro Gly Thr Ser Phe Arg Gly Thr Trp Ser Glu>

860 870 880 890 900
TGG AGT GAC CCC GTC ATC TTT CAG ACC CAG GCT GGG GAG CCC GAG GCA
ACC TCA CTG GGG CAG TAG AAA GTC TGG GTC CGA CCC CTC GGG CTC CGT
Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ala Gly Glu Pro Glu Ala>

910 920 930 940 950
GGC TGG GAC CCT CAC ATG CTG CTG CTC CTG GCT GTC TTG ATC ATT GTC
CCG ACC CTG GGA GTG TAC GAC GAC GAG GAC CGA CAG AAC TAG TAA CAG
Gly Trp Asp Pro His Met Leu Leu Leu Leu Ala Val Leu Ile Ile Val>

960 970 980 990 1000
CTG GTT TTC ATG GGT CTG AAG ATC CAC CTG CCT TGG AGG CTA TGG AAA
GAC CAA AAG TAC CCA GAC TTC TAG GTG GAC GGA ACC TCC GAT ACC TTT
Leu Val Phe Met Gly Leu Lys Ile His Leu Pro Trp Arg Leu Trp Lys>

1010 1020 1030 1040 1050
AAG ATA TGG GCA CCA GTG CCC ACC CCT GAG AGT TTC TTC CAG CCC CTG
TTC TAT ACC CGT GGT CAC GGG TGG GGA CTC TCA AAG AAG GTC GGG GAC
Lys Ile Trp Ala Pro Val Pro Thr Pro Glu Ser Phe Phe Gln Pro Leu>

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FIGURE 3C

1060 1070 1080 1090
TAC AGG GAG CAC AGC GGG AAC TTC AAG AAA TGG GTT AAT ACC CCT TTC
ATG TCC CTC GTG TCG CCC TTG AAG TTC TTT ACC CAA TTA TGG GGA AAG
Tyr Arg Glu His Ser Gly Asn Phe Lys Lys Trp Val Asn Thr Pro Phe>

1100 1110 1120 1130 1140
ACG GCC TCC AGC ATA GAG TTG GTG CCA CAG AGT TCC ACA ACA ACA TCA
TGC CGG AGG TCG TAT CTC AAC CAC GGT GTC TCA AGG TGT TGT TGT AGT
Thr Ala Ser Ser Ile Glu Leu Val Pro Gln Ser Ser Thr Thr Thr Ser>

1150 1160 1170 1180 1190
GCC TTA CAT CTG TCA TTG TAT CCA GCC AAG GAG AAG AAG TTC CCG GGG
CGG AAT GTA GAC AGT AAC ATA GGT CGG TTC CTC TTC TTC AAG GGC CCC
Ala Leu His Leu Ser Leu Tyr Pro Ala Lys Glu Lys Lys Phe Pro Gly>

1200 1210 1220 1230 1240
CTG CCG GGT CTG GAA GAG CAA CTG GAG TGT GAT GGA ATG TCT GAG CCT
GAC GGC CCA GAC CTT CTC GTT GAC CTC ACA CTA CCT TAC AGA CTC GGA
Leu Pro Gly Leu Glu Glu Gln Leu Glu Cys Asp Gly Met Ser Glu Pro>

1250 1260 1270 1280 1290
GGT CAC TGG TGC ATA ATC CCC TTG GCA GCT GGC CAA GCG GTC TCA GCC
CCA GTG ACC ACG TAT TAG GGG AAC CGT CGA CCG GTT CGC CAG AGT CGG
Gly His Trp Cys Ile Ile Pro Leu Ala Ala Gly Gln Ala Val Ser Ala>

1300 1310 1320 1330
TAC AGT GAG GAG AGA GAC CGG CCA TAT GGT CTG GTG TCC ATT GAC ACA
ATG TCA CTC CTC TCT CTG GCC GGT ATA CCA GAC CAC AGG TAA CTG TGT
Tyr Ser Glu Glu Arg Asp Arg Pro Tyr Gly Leu Val Ser Ile Asp Thr>

1340 1350 1360 1370 1380
GTG ACT GTG GGA GAT GCA GAG GGC CTG TGT GTC TGG CCC TGT AGC TGT
CAC TGA CAC CCT CTA CGT CTC CCG GAC ACA CAG ACC GGG ACA TCG ACA
Val Thr Val Gly Asp Ala Glu Gly Leu Cys Val Trp Pro Cys Ser Cys>

1390 1400 1410 1420 1430
GAG GAT GAT GGC TAT CCA GCC ATG AAC CTG GAT GCT GGC AGA GAG TCT
CTC CTA CTA CCG ATA GGT CCG TAC TTG GAC CTA CGA CCG TCT CTC AGA
Glu Asp Asp Gly Tyr Pro Ala Met Asn Leu Asp Ala Gly Arg Glu Ser>

1440 1450 1460 1470 1480
GGT CCT AAT TCA GAG GAT CTG CTC TTG GTC ACA GAC CCT GCT TTT CTG
CCA GGA TTA AGT CTC CTA GAC GAG AAC CAG TGT CTG GGA CGA AAA GAC
Gly Pro Asn Ser Glu Asp Leu Leu Leu Val Thr Asp Pro Ala Phe Leu>

1490 1500 1510 1520 1530
TCT TGT GGC TGT GTC TCA GGT AGT GGT CTC AGG CTT GGG GGC TCC CCA
AGA ACA CCG ACA CAG AGT CCA TCA CCA GAG TCC GAA CCC CCG AGG GGT
Ser Cys Gly Cys Val Ser Gly Ser Gly Leu Arg Leu Gly Gly Ser Pro>

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Figure 3D

1540 1550 1560 1570
GGC AGC CTA CTG GAC AGG TTG AGG CTG TCA TTT GCA AAG GAA GGG GAC
CCG TCG GAT GAC CTG TCC AAC TCC GAC AGT AAA CGT TTC CTT CCC CTG
Gly Ser Leu Leu Asp Arg Leu Arg Leu Ser Phe Ala Lys Glu Gly Asp>

1580 1590 1600 1610 1620
TGG ACA GCA GAC CCA ACC TGG AGA ACT GGG TCC CCA GGA GGG GGC TCT
ACC TGT CGT CTG GGT TGG ACC TCT TGA CCC AGG GGT CCT CCC CCG AGA
Trp Thr Ala Asp Pro Thr Trp Arg Thr Gly Ser Pro Gly Gly Gly Ser>

1630 1640 1650 1660 1670
GAG AGT GAA GCA GGT TCC CCC CCT GGT CTG GAC ATG GAC ACA TTT GAC
CTC TCA CTT CGT CCA AGG GGG GGA CCA GAC CTG TAC CTG TGT AAA CTG
Glu Ser Glu Ala Gly Ser Pro Pro Gly Leu Asp Met Asp Thr Phe Asp>

1680 1690 1700 1710 1720
AGT GGC TTT GCA GGT TCA GAC TGT GGC AGC CCC GTG GAG ACT GAT GAA
TCA CCG AAA CGT CCA AGT CTG ACA CCG TCG GGG CAC CTC TGA CTA CTT
Ser Gly Phe Ala Gly Ser Asp Cys Gly Ser Pro Val Glu Thr Asp Glu>

1730 1740 1750 1760 1770
GGA CCC CCT CGA AGC TAT CTC CGC CAG TGG GTG GTC AGG ACC CCT CCA
CCT GGG GGA GCT TCG ATA GAG GCG GTC ACC CAC CAG TCC TGG GGA GGT
Gly Pro Pro Arg Ser Tyr Leu Arg Gln Trp Val Val Arg Thr Pro Pro>

1780 1790 1800
CCT GTG GAC AGT GGA GCC CAG AGC AGC TAG
GGA CAC CTG TCA CCT CGG GTC TCG TCG ATC
Pro Val Asp Ser Gly Ala Gln Ser Ser ***>

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Figure 4A Human Ig heavy chain locus (total length $\approx 1\text{Mb}$, not drawn to scale):

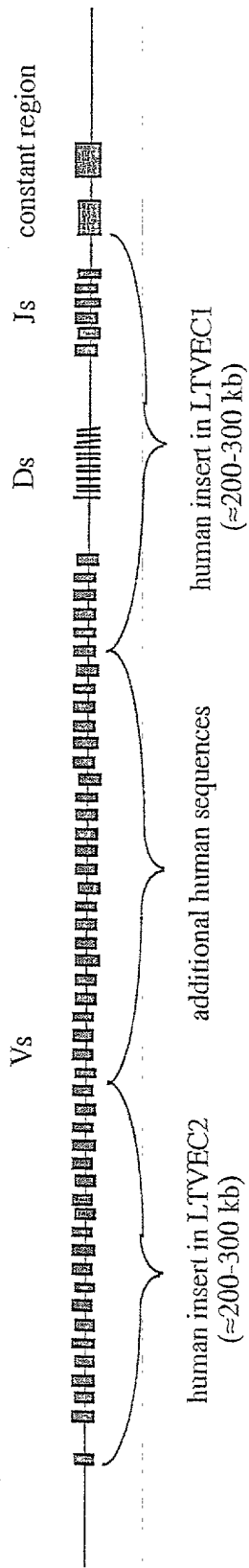


Figure 4B Mouse Ig heavy chain locus (total length $\approx 1\text{Mb}$, not drawn to scale) :

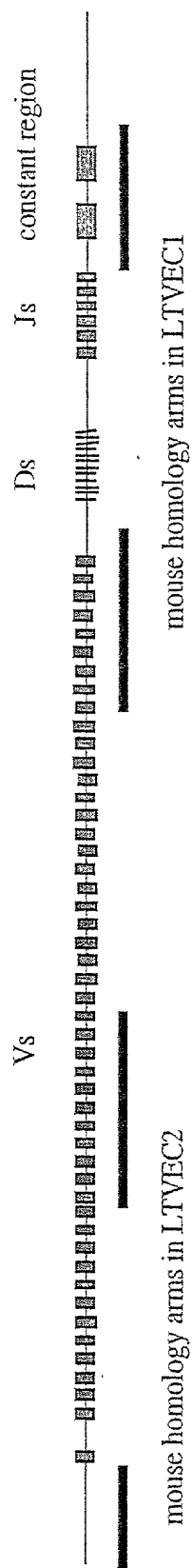


Figure 4C LTV2C2:

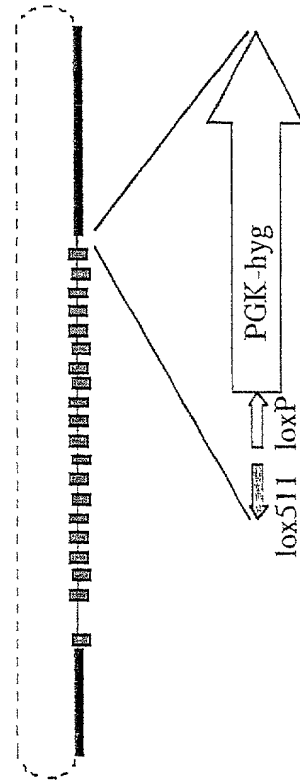


Figure 4d LTV2C1:

